Sir,

Haemorrhagic fever with renal syndrome caused by Puumala virus: evaluation of the risk for cataract formation

Puumala virus (PUU) infection, or nephropathia epidemica, is a systemic disease in the group of haemorrhagic fevers with renal syndrome causing ocular manifestations such as transient thickening of the crystalline lens.[1] PUU infection is most commonly found in northern Europe, but it has close relatives elsewhere, such as Korean haemorrhagic fever in Asia[2] and Hantavirus pulmonary syndrome in the United States.[3] A typical PUU infection begins abruptly with a high fever followed by headache, nausea, vomiting, backache and abdominal pain. Oliguria, or less commonly anuria, and subsequently polyuria result from the acute haemorrhagic tubular and interstitial nephritis. By 7–14 days the acute phase of the disease rapidly subsides, and convalescence leads to complete recovery within 1–2 months.[4–6] The infection causes permanent seropositivity and protective immunity.[7] The seroprevalence of PUU in the population has varied in different parts of Norway, Sweden and Finland from 1–5% up to 24%.[8-12]

Blurred vision is the most common ocular symptom associated with PUU infection, and transient myopia is its best recognised manifestation.[1,4–6,13–15] It is caused by myopic shift, the main mechanism for which is forward movement of the anterior ocular diaphragm and thickening of the crystalline lens.[1] Acute angle closure glaucoma attacks with markedly elevated intraocular pressure (IOP) during the acute phase of nephropathia epidemica are rather uncommon, although there are a few individual case reports.[13,16] In contrast, there are other reports describing a decrease in the IOP during the acute phase,[14,17] possibly resulting from diminished aqueous formation and filtration during the oliguric phase of the PUU infection.[17] Anterior uveitis and retinal haemorrhages have also been observed occasionally.[13,14]

The intraocular manifestations of PUU infection, especially the transient thickening of the crystalline lens[1] and intraocular hypotony,[17] and the fact that cataract is a multifactorial disease,[18] led us to the present seroepidemiological study. The primary purpose of this study was to determine out whether this viral disease represents a risk factor for cataract and, secondly, to evaluate the seroprevalence of PUU antibodies among the elderly population of Eastern Finland.

Patients and methods

Savonlinna Central Hospital is located in a lake region in which the incidence of nephropathia epidemica is considered to be the highest in Finland.[4] The study population comprised 351 individuals who were tested for the serum IgG antibodies to PUU; 176 of them were admitted to the hospital for cataract surgery, while the other 175 were control patients matched by age and sex and verified not to be suffering from cataract. Cataracts caused by ocular trauma, congenital factors, and syndromes associated with cataract (e.g. Down's syndrome) were excluded, as were patients with conditions predisposing to cataract formation, for example type 1 diabetes or alcoholism, and patients using systemic corticosteroids for a period of 1 year or more. There were 60 men and 116 women in the cataract group, and 59 men and 116 women in the control group. The mean age in the cataract group was 75.8 ± 9.1 years (range 46–94 years, median 77 years) and in the controls 75.4 ± 9.2 years (range 46–92 years, median 77 years). The age distribution of the patients showed that 133 of the 176 (75.6%) belonged to the oldest age groups, 70–99 years; the sex distribution of this group revealed a female predominance of 70.7% (94/133).

Sera were analysed by indirect immunofluorescent antibody assay and haemagglutination inhibition tests.[19] To analyse for statistical differences the chi-squared test, McNemar's test and analysis of variance were used. A p value of <0.05 was considered statistically significant in this study.

Results

Specific serum IgG antibodies to PUU were found in 106 of the 351 study subjects (30%). Fifty-nine (56%) of the 106 PUU-seropositive persons belonged to the cataract group ($n = 176$) and the remaining 47 (44%) to the non-cataractous control group ($n = 175$). The difference between the groups was not statistically significant ($p = 0.210$), nor was any gender predisposition for cataract revealed by serological testing (men: $p = 0.930$; women: $p = 0.120$). However, the seropositivity rate for men was statistically significantly higher (45%, 53/119) than for women (23%, 53/232), $p<0.001$. The sex ratio (M:F) of the seropositive individuals was 2:1. The mean age of seropositive men was 74.4 ± 10.1 years and of women 77.3 ± 9.1 years, with the respective values for seronegative men and women being 72.6 ± 10.2 years and 76.5 ± 8.1 years. The age differences between the seropositive and seronegative groups were not statistically significant. The detailed distribution of the seropositivity rate to PUU in different groups is presented in Table 1.

Discussion

The total seroprevalence to PUU in the present series, 30%, is the highest reported so far.[8–12] Therefore, this

Table 1. *Seroprevalence rate for Puumala virus IgG antibodies in men and women as well as in cataract patients and their controls in the series of 351 individuals*

	Seroprevalence	Significance
Men	53/119 (44.6%)	$p < 0.001$
Women	53/232 (22.8%)	
Cataract group	59/176 (33.3%)	$p = 0.21$
Non-cataractous controls	47/175 (26.9%)	
All participants	106/351 (30.2%)	

was a very appropriate area in which to conduct the current study.

Although no statistically significant difference in the seropositivity to PUU between the patients operated on for cataract and their controls was detected, this viral infection cannot be definitely excluded as a minor risk factor for cataract. This presumption is supported by the fact that in the acute phase of nephropathia epidemica one can find changes in intraocular dimensions, such as thickening of the crystalline lens[1] and intraocular hypotony.[17] The former is associated with cataract formation among diabetics[20] and the latter occurs after trabeculectomy.[21] Furthermore, it is known that sodium, potassium and calcium are important electrolytes in lens metabolism and cataractogenesis.[22,23] During PUU infection, the balance of these electrolytes in serum often fluctuates; for example the same patient may experience hypo- and hypernatraemia during different phases of the disease.[9] It is likely that such changes in serum electrolyte concentrations are reflected in the aqueous humour. Thus, changes in electrolyte and water balance may disrupt the functioning of the cation pump of the lens epithelium and hamper its ability to maintain the proper sodium and potassium balance between the aqueous humour and the lens. This hypothesis is supported by the observations of thickening of the lens during acute systemic PUU infection.[1]

The female predominance among the patients operated on for cataract supports previous reports that women suffer more from idiopathic cataract than men.[24,25] One explanation for the female predominance is the fact that, on average, women live longer than men in the study area (>70 years; 2711 men vs 5452 women, M:F = 1:2).[26] On the other hand, the female predominance among the patients operated on for cataract (>70 years; 39 men and 94 women, M:F = 1:2.4) does not support the hypothesis that there is a cataractogenic effect associated with nephropathia epidemica, because there was significantly more seropositivity to PUU in men. In this study, the high mean age of the patients undergoing cataract surgery was due to the exclusion of younger patients with a recognised aetiology of cataract.

The results of the present study suggest that there is a slight association between PUU infection and cataract formation even if no statistical significance was found.

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Sir,

Retinal neovascularisation and posterior penetrating ocular injury

Penetrating ocular injuries may induce a variety of haemorrhagic, inflammatory and structural sequelae, including proliferative vitreoretinopathy, sympathetic ophthalmitis, retinal detachment and intraocular haemorrhage. Despite an environment favouring the development of reparative fibrovascularisation, retinal neovascularisation following retinal detachment or trauma is uncommon. We present a case of unilateral peripheral retinal neovascularisation developing after posterior penetrating ocular trauma in the absence of other identifiable vasculogenic stimuli.

Case report

A 21-year-old white man sustained a penetrating injury of the right eye from a hand-held 7 cm spike whilst repairing a car. He underwent primary repair of a 4 mm circumferential nasal limbal wound with repositioning of prolapsed iris. There was no retained intraocular foreign body. Post-operative examination revealed a nasal retinal impact site with attached gel and a localised area of vitreous incarceration to the nasal limbal wound, although the retina was otherwise normal. The eye made an uneventful recovery, achieving 6/5 unaided vision.

Three months following the injury, peripheral retinal neovascularisation was identified in the right eye at the posterior border of the vitreous base. Fluorescein angiography revealed peripheral non-perfusion throughout 360° of the right eye with scattered peripheral sea-fan neovascularisation in all quadrants, but no vascular sheathing or features of vasculitis (Fig. 1). The left eye was normal to clinical and angiographic examination. Blood pressure, digital ophthalmodynamometry, full blood count, ESR, serum electrolytes, glucose, ACE, anticardiolipin antibody, haemoglobin electrophoresis, immunological tests, and investigations of the anticoagulant and fibrinolytic system were normal, although protein S was raised to 160% (normal range, 70–140%). The clinical appearance is unchanged at 3 years' follow-up.

Comment

Retinal neovascularisation develops in response to multiple extracellular modulating and cellular factors acting on endothelial cells at discontinuities in the basement membrane.[1] Such factors promote peripheral retinal neovascularisation in a variety of ischaemic and

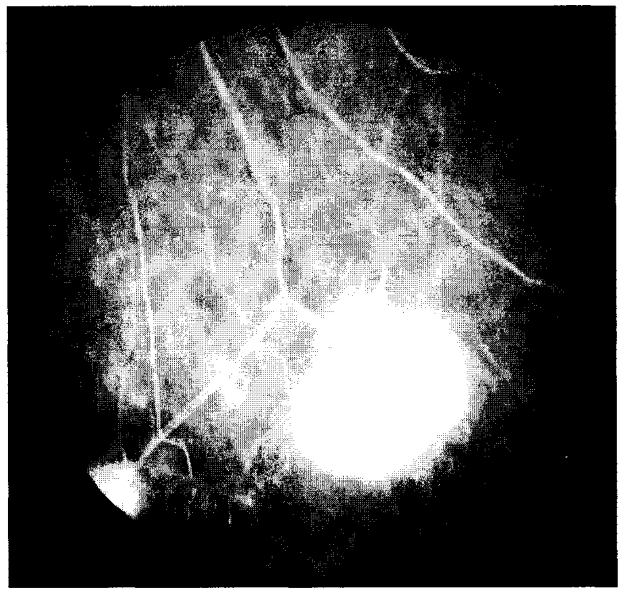

Fig. 1. *Fluorescein angiogram demonstrating peripheral non-perfusion and neovascularisation 'sea-fans'.*